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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,751	06/19/2006	Brad St Croix	001107.00526	8976

22907 7590 11/06/2008

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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
11/06/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/518,751	ST CROIX ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55, 57 and 60-63* is/are rejected.

7)☒ Claim(s) *56,58 and 59* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/21/04; 1/22/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of the Invention of Group I, claims 55-63 wherein the TEM protein is an inwardly-rectifying channel, subfamily J, member 8 in the reply filed on 21 July 2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 55-63 are pending and under consideration.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 21 December 2004 and 22 January 2007 have been fully considered by the examiner. A signed and initialed copy of each IDS is included with the instant Office Action.

Specification

4. The abstract of the disclosure is objected to because the abstract filed 25 October 2005 is drawn to a "Scroll Compressor" that does not appear to be relevant to the disclosed and claimed subject matter of the instant application. Correction is required. See MPEP § 608.01(b).

For convenience, Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

5. The disclosure is objected to because of the following informalities:

a. The specification at pg. 42 discloses U.S. Application No. 09/918,715, which is now U.S. Patent 7,402,660 and should be updated accordingly. Applciants' cooperation is requested in reviewing the specification for additional US Application serial numbers that require updating, i.e., "now abandoned" or "U.S. Patent…".

b. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict to the title to the claimed antibodies that bind the extracellular domain of the potassium-rectifying channel, subfamily J, member 8.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 57 and 60-63 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 57 is indefinite in the recitation "single chain variable region (ScFv)". Thos skilled in the art recognize that a ScFv is a single chain antibody in which a heavy chain variable region is linked via a peptide linker to a light chain variable region (see Bird et al, Science, 242(4877):423-426, October 21, 1988). Where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description

must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). The term "ScFv" in claim 57 is used by the claim to mean "single chain variable region", while the accepted meaning is an antibody light chain variable region linked to a heavy chain variable region via a peptide linker. The term is indefinite because the specification does not clearly redefine the term.

b. Claims 60-63 are indefinite in the recitation "is bound to…" in claims 60-63. The nature of the linkage of the recited moieties to the molecule is unclear. Do the molecules comprising a variable region bind to the therapeutic moieties of the claims such that they are "bound to" as presently recited, is the molecule comprising the variable region bispecific, e.g., binds the potassium inwardly-rectifying channel, subfamily J, member 8 and a therapeutic moiety, or are the therapeutic moieties linked or conjugated to the therapeutic moieties recited in the claims. As written, one skilled in the art would not reasonably be apprised of the metes and bounds of the claims.

Claim Rejections 35 USC §§ 101 and 112, First Paragraph

8. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 55-63 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility.

The claims of the instant invention are drawn to an isolated molecule comprising an antibody variable region that binds to an extracellular domain of the potassium inwardly-rectifying channel, subfamily J, member 8 (also known in the art as Kir6.1, KCNJ8, uKATR-1), wherein the molecule is an intact antibody, a single chain variable region, a humanized or human antibody and wherein the antibody is linked ("bound to") a therapeutic/detectable moiety. The disclosed asserted utilities for an antibody include using the antibody to inhibit neoangiogenesis, methods of inhibiting cancer growth through the inhibition of angiogenesis, identifying regions of neoangiogenesis, screening for neoangiogenesis and identifying endothelial cells, among others. The credibility of the asserted utilities has not been questioned. The specification has not taught the relationship of the potassium inwardly-rectifying channel, subfamily J, member 8 protein with any specific disease nor has the specification established any specific etiology of any specific disease that is associated with the potassium inwardly-rectifying channel, subfamily J, member 8 protein. As such, antibodies developed against the protein would also have no specific and substantial utility or well established utility. Besides the fact that the characterization of the protein has not been established, there is no evidence that the protein even exists in endothelial cells associated with tumor vasculature.

The specification discloses that through SAGE analysis, the applicants were able to discover genes that were differentially expressed in normal endothelial cells verses tumor associated endothelial cells, i.e., were expressed at 2-fold or higher. Through this analysis, several genes were up regulated in expression when normal endothelial cells where compared with tumor associated endothelial cells. Among these upregulated genes were potassium inwardly-rectifying channel, subfamily J, member 8, wherein the specification teaches that potassium inwardly-rectifying channel, subfamily J, member 8 expression was

unregulated in several tumor types. The specification asserts that the transcripts expressed at higher levels in tumor endothelium are most likely to be useful in the future for diagnostic and therapeutic purposes. Clearly, further research would be required of the skilled artisan to establish a nexus between the potassium inwardly-rectifying channel, subfamily J, member 8 protein and specific cancer types and whether and how the potassium inwardly-rectifying channel, subfamily J, member 8 protein could be used as diagnostic marker or therapeutic target. Such further experimentation indicates that the asserted utility is not in currently available form.

Furthermore, the literature indicates that such results are to be evaluated very critically. For example, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

Additionally, increased transcription does not always correlate with increased polypeptide levels. See Haynes et al (Electrophoresis 192:1862-1871, 1998), who studied more than 80 proteins relatively homogeneous in half-life and expression level, and found no strong correlation between protein and transcript level. For some genes, equivalent mRNA levels translated into protein abundances, which varied more than 50-fold. Haynes et al concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second par., and Fig. 1). Lian et al. (2001, Blood 98:513-524) show a similar lack of correlation in mammalian (mouse) cells (see p. 514, top of left column: “The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to

extrapolate directly from individual mRNA changes to corresponding ones in protein levels."). See also Fessler et al. (2002, J. Biol. Chem. 277:31291-31302) who found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291 , abstract). Additionally, Hanash S (Nature Reviews, Applied Proteomics Collection, pp. 9-14, March 2005) states "For example, a gene can be amplified 100-fold in certain tumors with no demonstrable effect on RNA levels for that gene." "Alternatively, protein levels can be increased, decreased or modified with no demonstrable changes in the levels of their corresponding RNAs." (see page 9). Hanash also indicates "no single type of molecular approach fully elucidates tumor behavior, necessitating analysis at multiple levels encompassing genomics and proteomics" (see abstract).

Therefore, data pertaining to potassium inwardly-rectifying channel, subfamily J, member 8 gene expression does not indicate anything significant regarding the claimed potassium inwardly-rectifying channel, subfamily J, member 8 polypeptide and antibodies, nor a role in neoangiogenesis. The data do not support the assertion that the potassium inwardly-rectifying channel, subfamily J, member 8 polypeptide and, in turn, antibodies thereto can be used as a cancer diagnostic or therapeutic agent. Significant further research would be required of the skilled artisan to reasonably confirm that the potassium inwardly-rectifying channel, subfamily J, member 8 is overexpressed in any cancer to the extent that it could be used as a cancer diagnostic or therapeutic agent, and thus, the asserted utility is not substantial. In the absence of information regarding whether or not potassium inwardly-rectifying channel, subfamily J, member 8 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the potassium inwardly-rectifying channel, subfamily J, member 8 polypeptide and antibody as diagnostic marker and therapeutic target is simply a starting point for further research and investigation into potential practical uses of the polypeptide. See *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "'The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[I]t is not a reward for the search, but compensation for its successful conclusion."

A probable utility does not establish a practical utility, which is established by actual testing or where the utility can be "foretold with certainty." *Bindra v. Kelly*, 206 USPQ 570, 575 (Bd. Pat. Inter. 1979) (Reduction to practice was not established for an intermediate useful in the preparation of a second intermediate with a known utility in the preparation of a pharmaceutical. The record established there was a high degree of probability of a successful preparation because one skilled in the art may have been motivated, in the sense of 35 U.S.C. 103, to prepare the second intermediate from the first intermediate. However, a strong probability of utility is not sufficient to establish practical utility.). Practical utility is a shorthand way of attributing "real-world" value to claimed subject matter. In other words, one skilled in the art can use a claimed discovery in a manner, which provides some immediate benefit to the public.

11. Claims 55-63 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 55, 57 and 60-63 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody comprising all six CDRs, three from the heavy chain and three from the light chain and binds antigen, wherein the antibody specifically binds to an extracellular domain of the potassium inwardly-rectifying channel, subfamily J, member 8, does not reasonably provide enablement for a molecule comprising an antibody variable region that does not comprise all six CDRs, three from the heavy chain and three from the light chain that specifically binds to an extracellular domain of the potassium inwardly-rectifying channel, subfamily J, member 8. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CAFC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention is engineered antibodies and cancer immunotherapy where the relative level of skill of those in the art is deemed to be high.

The claims are broadly dawn to a molecule comprising an antibody variable region that specifically binds an extracellular domain of the potassium inwardly-rectifying channel, subfamily J, member 8, wherein the molecule is a

single chain variable region and wherein the antibody is linked ("bound to") a therapeutic moiety. Thus, the claims encompass single variable domain antibodies that do not contain a full set of six CDRs, and do not bind antigen.

The specification discloses only antibodies comprising heavy chain variable regions that comprise CDR1, CDR2 and CDR3 and light chain variable regions that comprise CDR1, CDR2 and CDR3 and the antibody binds antigen. The specification does not disclose or provide a single working example of molecules that only comprise a heavy chain variable region or a light chain variable region, wherein the molecule binds antigen. Thus, the scope of the scope of the claims is extremely broad compared to the guidance and exemplification provided in the specification. The scope of the claims must bear a reasonable correlation with the scope of enablement. See *In re Fisher*, 166 USPQ 19 24 (CCPA 1970).

The state of the prior art is such that it is well established in the art that the formation of an intact antigen-binding site of antibodies routinely requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, Fundamental Immunology, 3rd Edition, 1993, pp. 292-295, under the heading "Fv Structure and Diversity in Three Dimensions"). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect

antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA, 79(6):1979-1983, March 1982). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Colman P. M. (Research in Immunology, 145:33-36, 1994) teaches that even a very conservative substitution may abolish binding or may have very little effect on the binding affinity (see pg. 35, top of left column and pg. 33, right column). Additionally, Bendig M. M. (Methods: A Companion to Methods in Enzymology, 1995; 8:83-93) reviews that the general strategy for "humanizing" antibodies involves the substitution of all six CDRs from a rodent antibody that binds an antigen of interest, and that all six CDRs are involved in antigen binding (see entire document, but especially Figures 1-3). Similarly, the skilled artisan recognized a "chimeric" antibody to be an antibody in which both the heavy chain variable region (which comprises the three heavy chain CDRs) and the light chain variable region (which comprises the three light chain CDRs) of a rodent antibody are recombined with constant region sequences from a human antibody of a desired isotype (see entire document, but especially Figures 1-3). Thus, the state of the art recognized that it would be highly unpredictable that a specific molecule comprising an antibody variable region but comprising less than all six CDRs of a parental antibody with a desired specificity would retain the antigen-binding function of the parental antibody. Thus, the minimal structure which the skilled artisan would consider predictive of the binding function includes six CDRs (three from the heavy chain variable region and three from the light chain variable region) in the context of framework sequences which maintain their correct spatial orientation have the requisite antigen binding function. It is unlikely that the molecules comprising only a heavy chain variable region, or comprising only a light chain variable region, which contains less than the full complement of CDRs from the heavy and light chain variable regions have the required binding function. Applicants have provided insufficient evidence or nexus that would lead the skilled artisan to predict the ability of using the recited

molecules containing fewer than 6 CDRs, resulting in a molecule that binds an extracellular domain of the potassium inwardly-rectifying channel, subfamily J, member 8 for anti-tumor therapy. One of skill in the art would neither expect nor predict the appropriate functioning of the altered heavy and light chain variable regions as broadly as is claimed.

In view of the lack of the predictability of the art to which the invention pertains as evidenced by Paul W. E. and Rudikoff et al, Colman P. M., and Bendig M. M., the lack of guidance and direction provided by applicant, and the absence of working examples, undue experimentation would be required to practice the claimed molecules comprising only an antibody variable region comprising less than the full complement of CDRs from the heavy and light chain variable regions, wherein the molecule binds an extracellular domain of the potassium inwardly-rectifying channel, subfamily J, member 8 with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed molecules and absent working examples providing evidence which is reasonably predictive that the claimed molecules bind an extracellular domain of the potassium inwardly-rectifying channel, subfamily J, member 8, commensurate in scope with the claimed invention.

14. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Blanchard/
Primary Examiner, A.U. 1643